R E M A R K S

Request for Form PTO-892

In item no. 7 on page 7 of the Office Action, claims were rejected over Azuma et al. (WO 00/09162). Since WO 00/09162 is presently not of record, the Examiner is respectfully requested to issue a Form PTO-892 which identifies WO 00/09162.

Information Disclosure Statements

The Office Action enclosed copies of the INFORMATION DISCLOSURE STATEMENTS BY APPLICANT IDS Forms dated May 16, 2005; the IDS Forms dated June 27, 2005; the IDS Forms dated August 16, 2007; and the IDS Form dated April 21, 2008, with the Examiner's initials next to some of the cited publications, indicating that all of the initialed cited publications were considered and made of record.

The Examiner drew lines through several of the publications cited on the aforesaid IDS Forms and labeled said publications as "not considered," for the reason that translations were not provided (see item no. 5 bridging pages 2 to 3 of the Office Action).

June 27, 2005 IDS Form

On sheet 2 of the June 27, 2005 IDS Form, the Examiner did not consider Nature, 389, pp. 990-994 (1997), although it is in English. It is respectfully requested that the Examiner consider and make of record this publication.

The above-identified application is a U.S. national phase application of International application PCT/JP03/14559. In the June 27, 2005 INFORMATION DISCLOSURE STATEMENT, a copy of an English-language International Search Report for PCT/JP03/14559 was submitted. All the publications identified on sheet 2 of the June 25, 2007 IDS Form were cited in the aforesaid English-language International Search Report for PCT/JP03/14559. All the publications which the Examiner drew lines through on the copy of the June 27, 2005 IDS Form were cited in said International Search Report for PCT/JP03/14559 and thus should have been considered and made of record by the Examiner. Pursuant to MPEP 609.04(a)III, a portion of which is reproduced hereinbelow:

MPEP 609.04(a)III provides as follows:

> "Where the information listed is not in the English language, but was cited in a search report or other action by a foreign patent office in a counterpart foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English-language version of the search report or action which indicates the degree of relevance found by the foreign office. This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an 'X,' 'Y' or 'A' indication on a search report."

Additionally, submitted concomitantly herewith are partial English-language translations of the following publications identified on sheet 2 of the June 27, 2005 IDS Form:

The Pharmaceuticals Monthly, 38(9), 2311-2331 (1996);
Ganka, 44, 1443-1448 (2002); and
Ganka, 44, 1458-1463 (2002).

It is therefore respectfully requested that a copy of said sheet 2 of the June 27, 2005 IDS Form be returned to the undersigned, with the Examiner's initials in the left column next to each publication, to indicate that each publication was considered and made of record.

With respect to Tokushige et al., Bio Clinica, 17(13) 1191-1994 that was cited on said sheet 2 of the June 27, 2005 IDS Form, it is noted that said document was published on December 20, 2002. Such document is not a reference against the present application, since, as discussed hereinbelow, the present application is entitled to its November 18, 2002 Japanese priority date.

August 16, 2007 IDS Form

On sheet 1 of the August 16, 2007 IDS Form, the Examiner did not initial US 2005/0245509 and USP 4,952,581. It is respectfully requested that the Examiner return another copy of sheet 1 of said August 15, 2007 IDS Form , with the Examiner's initials in the left column next to each of US 2005/0245509 and USP 4,952,581.

Claim Amendments

Claims 1 and 2 were amended to recite a Rho kinase inhibitor that was recited in original claim 1. Claims 1 and 2 were also amended to recite the terminology of "pharmaceutically effective amounts of," which is supported in the specification on page 7, lines 15 to 16 and page 8, line 2 to page 9, line 4. Claim 2 was also editorially amended to replace "characterized in that it" with --which--.

Editorial amendments were made to claim 6.

Rejection Under 35 USC 112, First Paragraph

Claims 1 to 4 were rejected under 35 USC 112, first paragraph, for allegedly failing to comply with the written description requirement for the reasons set forth in item no. 7 on pages 3 to 5 of the Office Action.

The position was taken in the Office Action that the term "Rho kinase inhibitor" is not adequately described as it is defined by a functional characteristic, and there is no evidence that there is any per se structure/function relationship between the disclosed four compounds and any others that might yet not be found. On the other hand, it was acknowledged in the Office Action that the specification provides written description for the four compounds recited in claim 3.

Claims 1 and 2 were amended to define the "Rho kinase inhibitor" as a specific compound recited in original claim 3, i.e., (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide (also known as "Y-39983").

In view of the above, withdrawal of the 35 USC 112, first paragraph rejection is respectfully requested.

Anticipation Rejection Under 35 USC 102

Claims 1 to 3 were rejected under 35 USC 102 as being anticipated by Dole et al. (US 2005/0014783) for the reasons stated in item no. 9 on pages 5 to 6 of the Office Action.

Submitted concomitantly herewith is an English-language translation of applicants' Japanese priority application 2002-333213 filed November 18, 2002, along with a statement of accuracy of translation (entitled "DECLARATION") signed by Mr. Akira Watanabe on February 4, 2009. Since applicants' Japanese priority application was filed before the earliest possible reference date for US 2005/0014783 (May 29, 2003) pursuant to MPEP 2136.05, withdrawal of US 2005/014783 as a reference is respectfully requested.

Withdrawal of the 35 USC 102 rejection is respectfully solicited.

Obviousness Rejections Under 35 USC 103

Claim 4 was rejected under 35 USC 103 as being unpatentable over Dole et al. (US 2005/0014783) and in view of Jin et al. (USP 6,187,304) for the reasons set forth in item no. 11 on pages 6 to 7 of the Office Action.

As discussed above, it was respectfully requested that US 2005/0014783 be removed as a reference. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1 to 4 were rejected under 35 USC 103 as being unpatentable over Azuma et al. (WO 00/09162) (USP 6,673,812) for the reasons indicated in item no. 12 on pages 7 to 8 of the Office Action.

Azuma et al. disclose the use of a Rho kinase inhibitor for treating glaucoma. Azuma et al., in columns 13 to 18, list over two hundred Rho kinase inhibitors, one of which is "Y-39983." In the BACKGROUND ART, in column 1, lines 39 to 42, Azuma et al. describe that beta-blockers, such as timolol are widely used for the treatment of glaucoma as they lower intraocular pressure ("IOP"). However, it was admitted in the Office Action that Azuma et al. do not expressly teach a composition comprising the combination of a Rho kinase inhibitor and a beta-blocker.

It was stated in the Office Action that it is obvious to combine two drugs known to be effective for the same purpose, in order to form a third composition that is to be used for the very same purpose.

For the following reasons, applicants respectfully disagree with the reason set forth in the preceding paragraph regarding the imposition of the obviousness rejection based on Azuma et al.

MPEP 2143 describe Exemplary Rationales (A) to (G) that may support a conclusion of obviousness. It is considered that the above obviousness is rejected based on Rationale (A), i.e., "combining prior art elements according to known methods to yield predictable results." However, MPEP 2143 describes that the Examiner must articulate "findings that one of ordinary skill in the art could have recognized that the results of the combination were predictable" to reject a claim based on rationale (A). It is demonstrated hereinbelow that the presently claimed invention

yields results that would not be predictable to one of ordinary skill in the art.

In Azuma et al., there is no teaching or suggestion of a combination of a Rho kinase inhibitor, let alone the specific Rho kinase inhibitor recited in applicants' present claims 1 and 2, and another therapeutic agent for glaucoma, let alone a beta-blocker. Moreover, it is reported that among various intraocular pressure reducing drugs, combinations of drugs that can be expected to theoretically have an additive effect are limited (see Ganka, 44, 1443-1448 (2002), a partial English-language translation of which is enclosed). Although it is reported that some combinations of therapeutic agents for glaucoma exhibit an additive effect, the following combinations are expected not to have an additive effect.

a) beta-blockers and alpha-2 agonists (see Ganka, 44, 1443-1448 (2002))

b) beta-blockers and sympathomimetics (e.g., epinephrine and dipivefrin) (see Ganka, 44, 1443-1448 (2002) and Ganka, 44 1458-1463 (2002), a partial English-language translation of each of which are enclosed)

c) pilocarpine and anticholineaterase (The Pharmaceuticals Monthly, 38(9) 2311-2331 (1996), a partial English-language translation of which is enclosed).

Accordingly, it is respectfully submitted that one of ordinary skill in the art would not necessarily expect desired results caused by a combination of therapeutic agents which individually are known for treating glaucoma, including beta-blockers. In particular, since at the time the present invention was made, there was no report regarding the combination of the

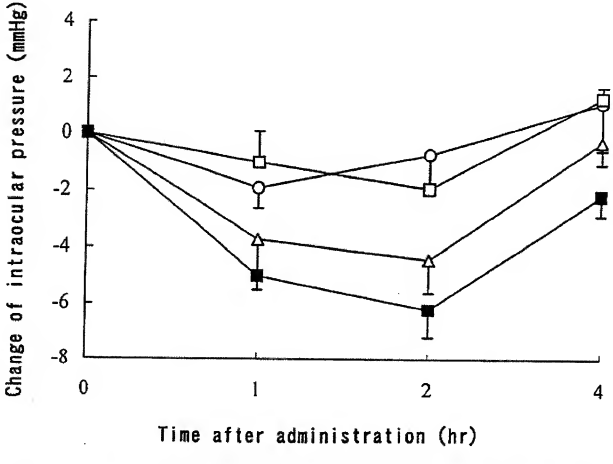
specific Rho kinase inhibitor recited in applicants' present claims 1 and 2, and any other therapeutic agent for glaucoma (such as a beta-blocker), its combined effect would not be predictable to one of ordinary skill in the art.

Therefore, it is respectfully submitted that one of ordinary skill in the art would not arrive at applicants' presently claimed invention from Azuma et al.

Moreover, while some combinations of therapeutic agents for glaucoma are reported to have an additive effect, it is noted that the presently claimed invention has a potent and a synergistic effect. As shown in Fig. 1 of the present application, the Rho kinase inhibitor ((R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide; "Compound A"; the specific Rho kinase inhibitor that is recited in applicants' present claims 1 and 2) single administration group exhibits little or no IOP reducing action, especially one and four hours after administration. On the other hand, in the Rho kinase inhibitor and beta-blocker combination administration group, IOP reduction and its persistence are much more potent than those of the beta-blocker single administration group.

Fig. 1 in applicants' application is reproduced as follows:

Fig. 1



■ : Rho kinase inhibitor(Compound A) and β-blocker(timolol) combination administration group

□ : Single administration group of Rho kinase inhibitor(Compound A)

△ : Single administration group of β-blocker(timolol)

○ : Control group

Accordingly, it is respectfully submitted that the combination of the specific Rho kinase inhibitor recited in applicants' present claims and a beta-blocker, such as timolol, yield unpredictable results.

Withdrawal of the 35 USC 103 rejection based on Azuma et al. is therefore respectfully requested.

Claims 1 to 4 were rejected under 35 USC 103 as being unpatentable over DeSantis (USP 5,502,052) in view of Kapin (WO 97/23222) for the reasons set forth in item no. 13 beginning at the bottom of page 8 and continuing to the top of page 10 of the Office Action.

It was admitted in the Office Action that DeSantis does not expressly teach a composition with the combination of a Rho kinase inhibitor and a beta-blocker.

DeSantis teach only a combination of apraclondine and timolol to control intraocular pressure. As discussed above, DeSantis does not teach a composition comprising the combination of a Rho kinase inhibitor and a beta-blocker.

Kapin et al. teach a composition comprising an isoquinolinesulfonyl compound, such as fasudil for the treatment of glaucoma. Kapin et al. do not teach that the Rho kinase inhibitor recited in applicants' present claims 1 and 2 can be used for the treatment of glaucoma. Moreover, Kapin et al. do not teach or suggest that fasudil inhibits Rho kinase and that Rho kinase inhibitors lower intraocular pressure ("IOP"). Therefore, it is respectfully submitted that based on the disclosures of DeSantis and Kapin et al., a person having ordinary skill in the art would not arrive at a composition comprising the combination of the Rho kinase inhibitor recited in

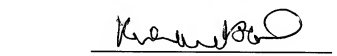
applicants' present claims 1 and 2 and a beta-blocker for the treatment of glaucoma.

Withdrawal of the above 35 USC 103 rejection is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



RICHARD S. BARTH
REG. NO. 28,180

FRISHAUF, HOLTZ, GOODMAN & CHICK, P.C.
220 FIFTH AVENUE, 16th FLOOR
NEW YORK, NEW YORK 10001-7708
Tel. Nos. (212) 319-4900
(212) 319-4551/Ext. 219
Fax No. (212) 319-5101
E-Mail Address: BARTH@FHGC-LAW.COM
RSB/ddf

Encs.: (1) partial English-language translation of The Pharmaceuticals Monthly, 38(9) 2311-2331 (1996)

(2) partial English-language translation of Ganka, 44, 1443-1448 (2002)

(3) partial English-language translation of Ganka, 44, 1458-1463 (2002)

(4) English-language translation of JP 2002-333213 and statement of accuracy of translation (entitled "DECLARATION") dated February 4, 2009